Expanding NEURON extracellular reaction-diffusion support: simulation of ischemic stroke

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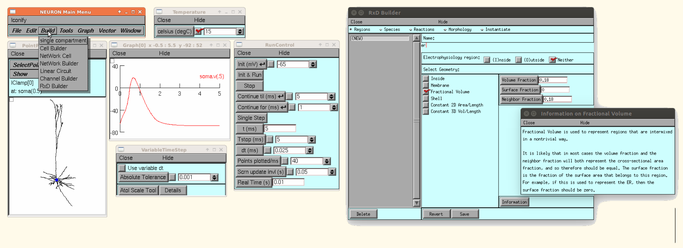
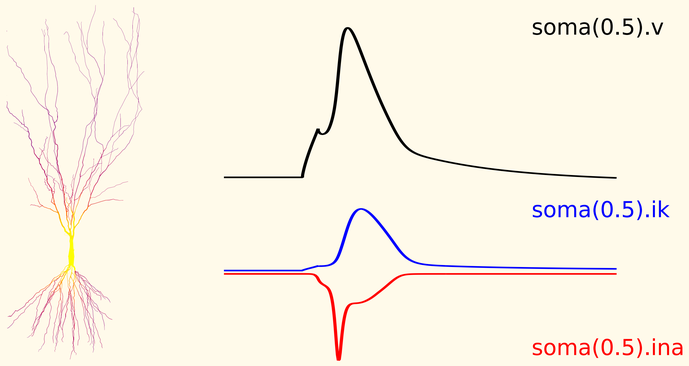
NEURON simulation platform

The NEURON simulation platform, featured in over 1900 publications, traditionally focused on models of neurons and networks of neurons.



Electrophysiology

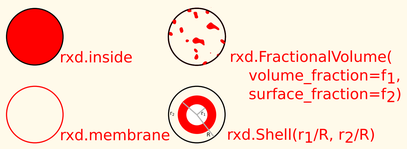


(ModelDB: 126814, Safiulina et al. Frontiers in synaptic neuroscience 2010)

Reaction-diffusion (*rxd*)

NEURON's reaction-diffusion module (*rxd*) expanded support for 1D and 3D intracellular reaction-diffusion models.

Where?



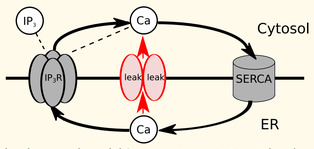
r = rxd.Region(apicals, geometry=???)

Who?

ca = rxd.Species([cyt, er], name='ca', charge=2)

(McDougal et. al. Frontiers in neuroinformatics 2013)

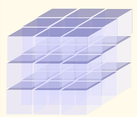
What?



leak = rxd.MultiCompartmentReaction(ca[er], ca[cyt], kf, kb, membrane=ermem)

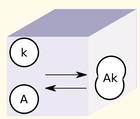
Extracellular

The *rxd* module has been extended to include coarse-grained macroscopic models of the extracellular space.



ecs = rxd.Extracellular(xlo=--30,ylo=-30,zlo=-30, xhi=30,yhi=30,zhi=30,dx=20, tortuosity=1.6,volume_fraction=0.2)

buffer = rxd.Reaction(A + k, AK, kf, kb)



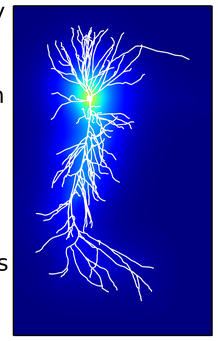
(Newton et. al. Frontiers in neuroinformatics *submitted*)

We continue to improve NEURON's reaction-diffusion support. Current work focuses on; 1. improving the performance, 2. stochastic simulations, 3. extending the GUI tools, 4. increasing adoption by external users.

Extracellular space

Objects in the extracellular space are represented by the tissue diffusion characteristics;
- **free volume fraction** (porosity)
- **tortuosity** (the average multiplicative increase in path length of a diffusing particle).

The *rxd* modules supports;
- anisotropy
- heterogeneous tissue characteristics
- Dirichlet (fixed concentration) boundary conditions
- Neumann (zero flux) boundary conditions.



$$1 - \frac{r_x}{2}\nabla_x^2\phi^{\left(t+\frac{1}{3}\right)} = \left(\frac{r_x}{2}\nabla_x^2 + r_y\nabla_y^2 + r_z\nabla_z^2\right)\phi^{(t)}$$

$$1 - \frac{r_y}{2}\nabla_y^2\phi^{\left(t+\frac{2}{3}\right)} = -\frac{r_y}{2}\nabla_y^2\phi^{\left(t+\frac{1}{3}\right)}$$

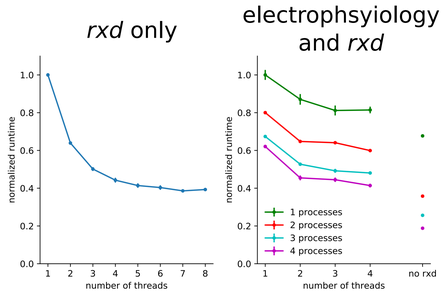
$$1 - \frac{r_z}{2}\nabla_z^2\phi^{(t+1)} = -\frac{r_z}{2}\nabla_z^2\phi^{\left(t+\frac{2}{3}\right)}$$

Diffusion is implemented using **Douglas Gunn Alternating Direction Implicit method**. An efficient O(N), unconditionally stable and trivial parallelizable finite volume method.

Performance

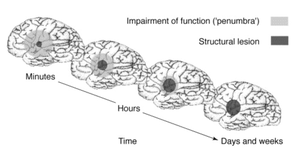
While the interface is in Python, numerical integration is performed by compiled C code. Performance is improved with **Just-In-Time** compilation of reaction.

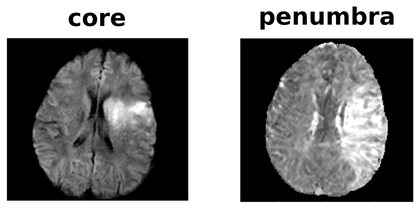
Extracellular reaction-diffusion benefits from two forms of parallelization; **multithreading** and **multiprocessor**.



Ischemic stroke

Ischemic stroke is a multiscale phenomena, with temporal scales from milliseconds to years and spatial scales from subcellular compartments to regions of the brain.



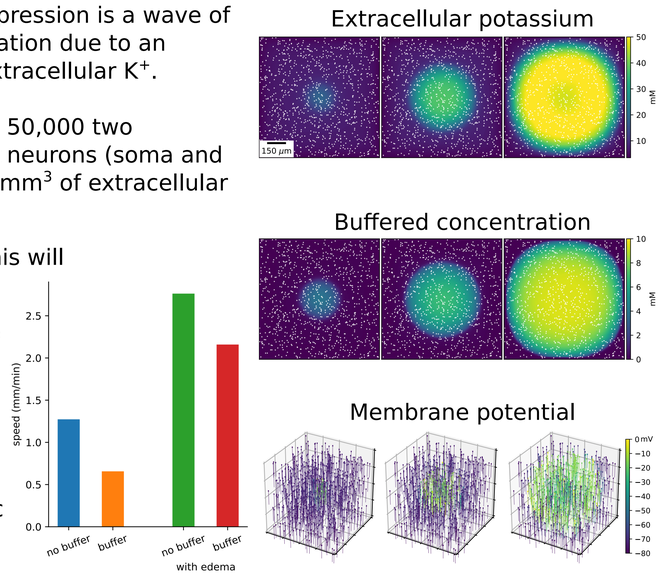


Spreading depression

Spreading depression is a wave of cell depolarization due to an increase in extracellular K^+.

We simulated 50,000 two compartment neurons (soma and dendrite) in $1mm^3$ of extracellular space.

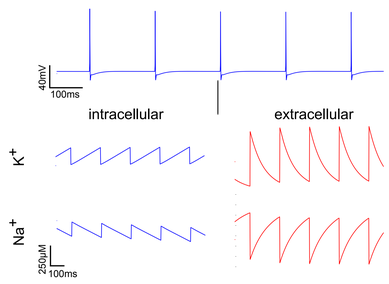
Models like this will enable us to develop the hypothesis of **multiple penumbrae**, created by diffusion and clearance of different toxic agents.



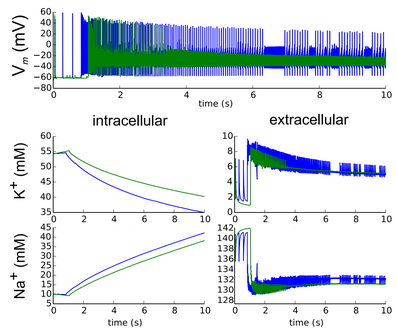
Cellular and sub-cellular scales

We add **Na^+/K^+-pumps** to a detailed multiscale model of a cortical pyramidal neuron (ModelDB: 189154).

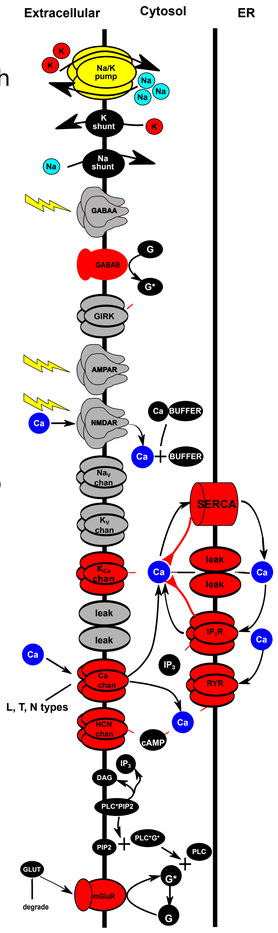
We maintain intracellular ion concentrations with **shunts**. This is a novel approach as concentration changes are usually ignored.



The pump rate depends on the available ATP, so reducing the available **ATP** caused the pump to fail and the cell to depolarize.



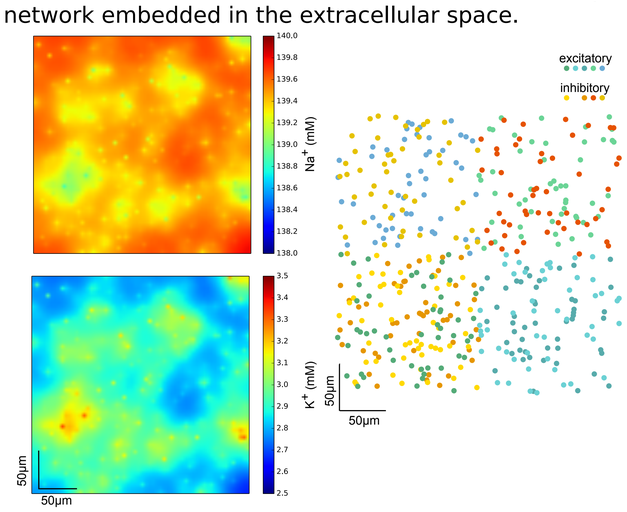
We will develop this biophysically detailed model to test **cellular patterning** of damage, where difference in surface to volume ratio and in the ER make parts of cell more susceptible to damage.



(Adapted from Frontiers in Pharmacology 2016).

NetPyNE

NetPyNE facilitates network development and analysis. Network models will allow us to study distant excitotoxicity resulting from synaptic activation from mini-seizure centers. Here is an example of a multilayer network embedded in the extracellular space.



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Newton AJH, et al. "Using NEURON to promote reproducibility in reaction-diffusion modeling of extracellular dynamics." Frontiers in neuroinformatics. (submitted).
Neymotin, AA., et al. "Multitarget multiscale simulation for pharmacologicaltreatment of dystonia in motor cortex." Frontiers in Pharmacology 7 (2016).
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